TYROSINE AVAILABILITY: A PRESYNAPTIC FACTOR CONTROLLING CATECHOLAMINE RELEASE

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Considerable evidence has been available for many years that low doses of exogenous tryptophan, which elevate brain tryptophan but keep its levels within their normal range, can increase brain serotonin and 5-hydroxyindoleacetic acid concentrations (Wurtman and Fernstrom, 1976; Fernstrom and Wurtman, 1971). Moreover, food consumption had been shown some years ago to influence brain tryptophan, and thereby brain serotonin levels, with carbohydrate-rich meals increasing (Fernstrom and Wurtman, 1971) and protein meals decreasing (Fernstrom and Wurtman, 1972) serotonin synthesis, and it has been proposed that this coupling of food composition to serotonin synthesis allows serotonin-dependent behaviors to be affected by eating (Fernstrom and Wurtman, 1974; Young, 1983).

It was also found more than a decade ago, that consumption of supplemental tyrosine (Wurtman et al., 1974) or choline (Cohen and Wurtman, 1975; Haubrich et al., 1975) could affect the syntheses of their neurotransmitter products, the catecholamines and acetylcholine. However these responses were, until recently, poorly characterized, and were observed to be considerably less consistent than that of serotonin to supplemental tryptophan: Tyrosine administration only sometimes increased brain levels of catecholamine metabolites, and even then it failed to affect those of dopamine or norepinephrine; choline administration only sometimes affected brain acetylcholine levels (Blusztajn and Wurtman, 1983), and there was no acetylcholine metabolite to measure as evidence that more acetylcholine molecules were turning over. Moreover, no direct evidence was available that administration of tyrosine or choline could enhance either the release of their neurotransmitter, nor the postsynaptic responses to the transmitters.

This article summarizes evidence accumulated during the past decade that tyrosine availability can indeed affect catecholamine synthesis and release. It also comments on possible uses of supplemental tyrosine to amplify catecholamine-mediated neurotransmission, and thereby affect performance.

Early Studies Relating Tyrosine to Catecholamine Production

The failure of tyrosine administration to increase brain levels of its neurotransmitter products had led virtually all investigators to assume that tyrosine hydroxylase was fully saturated with its amino acid substrate *in vivo*, - this in spite of the fact that estimates of the enzyme's Km for

TABLE 1: Tyrosine Levels in Tissues and Fluids

Species	Tissue or Fluid	[Tyrosine]	Comments	Reference
Rat	Brain	47-65 nmol/g	Fasted	Fernstrom & Faller, 1978; Glaeser et al. 1983.
Rat	Brain	47-173 nmol/g	Non-fasted	Carlsson & Lindqvist, 1978; Fernstrom & Faller, 1978; Glaeser et al., 1983.
Rat	Plasma	70±80 μM	Adult	Brosnan et al., 1984; Chirigos et al. 1960.
Rat Fern-	Plasma	188±21 μM	Neonatal	Fernstrom & strom, 1981.
Rat Fern-	Plasma	233±2 μM	Fetal	Fernstrom & strom, 1981.
Dog Fern-	CSF	16±3 μM	-	Fernstrom & strom, 1981.
Primate	CSF	4-5 μM	Males, females	Young & Ervin, 1984.
Human	CSF	8-10 μM	Normal	Fernstrom & Fernstrom, 1981; Hagenfeldt et al., 1984; Perry et al., 1975.
Human	CSF	19-20 μM	Parkinsonian	Growdon et al., 1982.
Human	Plasma	50-60 μM	Normal, fasting	Hagenfeldt et al., 1984; Perry et al., 1975.

tyrosine in vitro [50 to 125 μM, depending upon whether tetrahydrobiopterin or a synthetic alternate was used as the cofactor (e.g., Morgenroth et al., 1975; Joh et al., 1978)] were not very much lower than whole-brain tyrosine

levels [which vary between 100 and 200 μM, depending on the protein content of the meal most recently consumed (Table 1)]. Catecholamines were, however, known to be stored within multiple metabolic compartments, including some with slow turnover times; this raised the possibility that supplemental tyrosine might actually accelerate the synthesis of a particular "pool" of dopamine or norepinephrine, but that this pool constituted too small a fraction of the total catecholamine store to allow detection. Hence experiments were performed to determine whether changes in tyrosine levels might affect rates of catecholamine synthesis, as estimated from the accumulation of dihydroxphenylalanine (DOPA) in brains of animals pretreated with a decarboxylase inhibitor (Wurtman et al., 1974; Carlsson and Lindqvist, 1978). Under such conditions, DOPA accumulation was shown to be accelerated when brain tyrosine levels were increased (by giving rats tyrosine), and diminished when tyrosine was reduced [by giving rats other large neutral amino acids, like tryptophan, valine, or parachlorophenylalanine, which compete with tyrosine for passage across the blood-brain-barrier (Pardridge, 1971)]. Such observations provided estimates of the Km for tyrosine's hydroxylation in vivo and showed that this process could indeed be affected when tyrosine levels varied within their normal range. However, the use of a decarboxylase inhibitor - which also diminishes catecholamine synthesis in nerve terminals - rendered problematic the extrapolation of these data to physiologic states, since the drug probably also reduced both the end-product inhibition of tyrosine hydroxylase and the release of newly-formed catecholamine into synapses. What was needed was an experimental approach that allowed catecholamine synthesis to be estimated, in the presence of varying brain tyrosine concentrations, without concurrently disturbing that synthesis. When one such approach was tried - that of measuring dopamine metabolites in striata of animals given tyrosine - no effect of tyrosine was observed (Scally et al., 1977), [although tissue dopamine levels were subsequently shown to rise in striata and cortices of rats given large doses of tyrosine methyl-esther (Oishi and Szabo, 1984)]. However, if the animals were concurrently given haloperidol, a dopamine receptor antagonist that accelerates nigrostriatal firing (Bunney et al., 1973) and can lower tyrosine levels in striata (Westerink and Wirix, 1983), catecholamine production did exhibit precursor dependence: striatal levels of homovanillic acid (HVA) varied directly with those of brain tyrosine, while dopamine levels themselves remained constant (Scally et al., 1977). These observations were interpreted as indicating that a given catecholaminergic neuron might or might not be responsive to having more or less tyrosine, depending on its level of activity.

The ability of tyrosine supplementation to enhance the synthesis of catecholamines in, and their release from rapidly firing neurons, (but not from relatively quiescent cells) has since been affirmed using a variety of experimental manipulations (Table 2): Thus, tyrosine administration increases brain levels of the norepinephrine metabolite methoxy-hydroxyphenylethylglycol sulfate (MHPG-SO4) in cold-stressed rats (Gibson and Wurtman, 1978) and in brains and brainstems of spontaneously hypertensive rats (SHR's) (Sved et al., 1979; Yamori et al., 1980) but not in those of control, normotensive animals, nor in SHR's given both tyrosine and another large neutral amino acid, valine (Sved et al., 1979), which competes with tyrosine for uptake into the brain (Pardridge, 1971). Increases in MHPG-SO4 after tyrosine treatment have also been observed in rats given yohimbine (Gibson, 1977), an alpha$_2$ antagonist, or in animals stressed by tail-shock (Reinstein et al., 1984). DOPA accumulation (after decarboxylase inhibition) is accelerated following tyrosine administration in straita of rats given gamma-butyrolactone (Sved and Fernstrom, 1981) (which blocks dopamine's release and the consequent activation of presynaptic inhibitory autoreceptors), and in the median eminence of animals that received exogenous prolactin (Sved, 1980) (which presumably activates the tuberoinfundibular dopaminergic neurons via a short feedback loop). Following a lesion

TABLE 2: Tyrosine Administration and Catecholamine Synthesis and Release

Tissue	Treatment	Biochemical Index	Tyrosine Effect	Reference
Striatum	Haloperidol	DOPAC, HVA	+60%	Scally et al., 1977.
Striatum, Limb. forb.	Haloperidol	DOPA	+15%	Carlsson and Lindqvist, 1978; Westerink and Wirix, 1983.
Striatum	NS tract lesions	DOPAC, HVA	+60%	Melamed et al., 1980.
Striatum	γ-butyrolactone	DOPA	+25%	Sved and Fernstrom, 1981.
Whole brain	Cold stress	MHPG-SO_4	+70%	Gibson and Wurtman, 1978.
Whole brain	SHRs	MHPG-SO_4	+40%	Sved et al., 1979.
Brainstem, forebrain	SHRs	MHPG-SO_4	+15%	Yamori et al., 1980.
Striatum, hypothalamus	Reserpine	DOPAC,HVA	+40%	Sved et al., 1979.
Whole brain	Yohimbine	MHPG-SO_4	+35%	Gibson, 1977.
Med. eminence	Prolactin	DOPA	+30%	Sved, 1980.
Hippocampus, hypothalamus	Tail shock	MHPG-SO_4	+40%	Reinstein et al., 1984.
Whole brain	Amfonelic acid, spiperone	DOPAC	+30%	Fuller and Snoddy, 1980.

that destroys about 80% of the nigrostriatal tract unilaterally [and thus accelerates the firing of the surviving neurons (Agid et al., 1973)] tyrosine administration increases dopamine release on the lesioned side, as estimated from the ratios of dihydorxyphenylacetic acid (DOPAC) or HVA to dopamine, or to tyrosine hydroxylase activity, but fails to affect either index on the intact side (Melamed et al., 1980). The tyrosine effect is, once again, blocked by valine, and is unassociated with changes in dopamine levels. Tyrosine administration also increases brain levels of dopamine metabolites in animals pretreated with reserpine (Sved et al., 1979), amfonelic acid, or spiperone (Fuller and Snoddy, 1980), all of which, like haloperidol, are thought to accelerate nigrostriatal firing; in prefrontal and cingulate cortex a low dose of tyrosine also increaes dopamine levels in animals not concurrently receiving drug treatments (Tam and Roth, 1984). Tyrosine increases levels of dopamine metabolites in light-activated rat retinas <u>in vivo</u> (Gibson et al., 1983), but not when animals are in darkness.

Tyrosine, Nigrostriatal Firing, and Dopamine Release

Direct evidence that physiologic variations in tyrosine availability can affect dopamine release has recently been obtained using an experimental system in which superfused slices of rat striatum are subjected to electrical pulses (20 Hz, 2ms) of varying train length; the amount of endogenous dopamine released into the medium is correlated with its tyrosine concentration.

Tissues are subjected to two trains of 600 or 1800 pulses, each lasting 30 or 90 seconds respectively, and separated by 30 minutes; dopamine release during the second (S2) period is expressed as a decimal fraction of the amount released during the initial (S1) period. When slices are superfused with Krebs bicarbonate buffer (which lacks tyrosine or any other amino acid), the S2/S1 ratio is 0.75-0.80, depending on the number of pulses (that is, dopamine release during S2 declined by 20-25%). A tyrosine concentration in the superfusate of at least 20 μM is needed to maintain an S2/S1 ratio of unity in slices stimulated for 30 seconds, while at least 40 μM is needed in tissues stimulated for 90 seconds. Tissues that have been stimulated while superfused with the tyrosine-free buffer display major reductions in tyrosine content (up to 50%), as well as in dopamine itself (25%) (Milner and Wurtman, 1984; Milner and Wurtman, in press).

Since dopaminergic terminals comprise only a small percentage of the total cellular mass of the striatum, this major depletion of striatal tyrosine suggets either that the amino acid becomes depleted within non-catecholaminergic cells, as well as within these terminals, or that most of the tyrosine normally present in the striatum is confined within dopaminergic terminals. In experiments designed to examine the latter possibility, these terminals were destroyed unilaterally by injecting the neurotoxin 6-hydroxydopamine into the substantia nigra. Even though the dopamine content of the ipsilateral striatum was depleted by more than 95%, its tyrosine levels were unchanged, indicating that striatal tyrosine is not preferentially localized within the dopaminergic terminals, and suggesting that the tyrosine depletion that occurred when the superfused slices were stimulated reflected mobilization of the amino acid from non-dopaminergic as well as from dopaminergic cells.

In vivo, dopaminergic nerve terminals are, of course, perfused not with a tyrosine-free solution but with tyrosine-containing blood; moreover, as discussed below, circulating tyrosine is able to enter the brain, its entry catalyzed by a facilitated diffusion system that it shares with other large, neutral amino acids (Pardridge, 1971). Hence it would not be expected that even the prolonged conversion of tyrosine to dopamine would cause its depletion, at least to the extent seen in vitro. However, the rate at which tyrosine diffuses from the plasma into dopaminergic nerve terminals is retarded both by the amino acid's limited water-solubility and by competition between it and other circulating amino acids for attachment to the blood-brain barrier transport site (Pardridge, 1971) and to neuronal membranes (Guroff et al., 1961). Hence the possibility remains that tyrosine in nerve terminals may fall, after prolonged neuronal firing, to levels sufficient to slow catecholamine synthesis. In that circumstance the ability of supplemental tyrosine to enhance catecholamine synthesis would be explained not so much by its ability to increase the substrate-saturation of tyrosine hydroxylase but by blocking the decrease that would otherwise occur. The inability of striatal dopaminergic terminals to sustain transmitter output without exogenous tyrosine contrasts with the ability of cholinergic neurons in the same tissue to continue making their neurotransmitter even when exogenous choline is lacking. Cholinergic terminals continue to release unchanged amounts of acetylcholine, even after 30 minutes of continuous stimulation, when superfused with the Krebs solu-

tion (which also, of course, lacks choline) (Maire and Wurtman, in press). The source of choline for this acetylcholine synthesis is probably a "reservoir" in the form of membrane phosphatidylcholine (PC) (Wurtman et al. 1985); the PC is hydrolyzed to free choline, which is then released into the extracellular space and then taken back up into the cholinergic terminal for acetylation. Apparently the protein in nerve terminals is unable to serve in an analogous manner as a reservoir for tyrosine.

Tyrosine and Sympatho-Adrenal Cells

Tyrosine availability has also been shown to affect catecholamine synthesis in peripheral tissues. Its acute or chronic (8 days) administration to cold-exposed rats caused dose-related increases in urinary norepinephrine and epinephrine (Alonso et al., 1980); valine or leucine failed to elicit similar responses, and, when administered with tyrosine, blocked the increases (Agharanya and Wurtman, 1982). The increase in urinary epinephrine was also blocked by bilateral adrenalectomy (Agharanya and Wurtman, 1982). In contrast, the rise in urinary norepinephrine was amplified in rats whose sympathetic terminals had been partially destroyed by prior administration of 6-hydroxydopamine (Agharanya and Wurtman, 1982), suggesting that an increase in their firing rates had occurred, rendering them more responsive to the amino acid. Tyrosine administration also caused increases in urinary dopamine; these were unaffected by adrenalectomy or 6-hydroxydopamine. Administration of oral tyrosine (33 mg/kg prior to each meal) to human subjects also increased urinary levels of the three catecholamines (Agharanya et al., 1981). After a single dose of the amino acid (100 or 150 mg/kg), urinary levels of the catecholamines and their principal metabolites all increased, with time-courses that paralleled the rise in blood tyrosine levels (Alonso et al., 1982). These observations were interpreted as suggesting that, in humans, both central and sympathoadrenal catecholamine synthesis are precursor-responsive.

Enhancement of sympathoadrenal catecholamine synthesis underlies tyrosine's ability to restore blood pressure in rats in hemorrhagic shock (Conlay et al., 1981). This response is blocked by bilateral adrenalectomy, performed immediately prior to testing (Conlay et al., 1981), or by pretreatment with carbidopa or phentolamine (Conlay et al., 1985), and is not simulated by other large neutral amino acids (like valine or leucine) (Conlay et al., 1985). [Tyrosine administration to hypotensive rats also elevates levels of epinephrine in the adrenal medulla, and of norepinephrine in the spleen (Conlay et al., 1985)]. That tyrosine's pressor effect is not mediated by its conversion to the sympathomimetic amine tyramine was demonstrated by its lack of effect (unlike tyramine) in rats receiving a ganglionic blocker (hexamethonium); its persistent pressor activity (again unlike tyramine) in reserpinized hypotensive rats; and its failure to elevate plasma tyramine levels when raising blood pressure (Conlay et al., 1984).

The fact that a given dose of tyrosine can raise blood pressure in hypotensive animals, lower it in spontaneously-hypertensive rats, and have little or no effect in normotensive animals (or people) has been interpreted as resulting from tyrosine's ability to enhance catecholamine synthesis only in neurons (or chromaffin cells) undergoing prolonged physiological activity: in hypotensive rats, the sympathoadrenal cells are active, and thus tyrosine-responsive; hence giving the amino acid potentiates their release of catecholamines, restoring blood pressure. In SHR, these peripheral neurons may be negatively quiescent, suppressed by the now-active brain-stem noradrenergic neurons that control sympathetic outflow (Philippu et al., 1980); hence tyrosine administration, by enhancing norepinephrine synthesis within the brain stem, further reduces sympathetic activity, causing blood pressure to fall. The possible utility of oral

tyrosine in treating hypertension is currently under investigation (Bossy et al., 1983); its use in treating shock (which would require parenteral administration) is hampered by its very poor water-solubility.

Plasma and Tissue Tyrosine

Published data on the levels of tyrosine in various tissues and body fluids are summarized in Table 1 (Brosnan et al., 1984; Fernstrom and Fernstrom, 1981; Young and Ervin, 1984; Hagenfeldt et al., 1984; Perry et al., 1975; Growdon et al., 1982; Chirigos et al., 1960). Tyrosine recently taken up from the extracellular space may be used preferentially for dopamine synthesis (Kapatos and Zigmond, 1977) (i.e., in contrast to tyrosine already present in the cytoplasm). This would allow acute changes in the plasma amino acid pattern to have relatively more of an effect on the synthesis and release of this neurotransmitter. The constituents of the plasma that affect brain tyrosine are not only the amino acid itself, but also the other large, neutral amino acids (LNAA, primarily tryptophan, phenylalanine, valine, isoleucine, and leucine) that compete with tyrosine for entry into the brain (Pardridge, 1971; Chirigos et al., 1960). Brain tyrosine levels sometimes correlate only poorly with plasma tyrosine concentration (e.g., after a protein-rich meal) but apparently are always well-correlated with the "plasma tyrosine ratio" (to other LNAA) (Fernstrom and Faller, 1978). Hence, an increase in plasma levels of the branched-chain amino acids - such as would result from insulin deficiency or insensitivity - could decrease both the transport of tyrosine across the blood-brain-barrier, and its subsequent conversion to catecholamines. Both dietary (Fernstrom and Faller, 1978; Glaeser et al., 1983) and pharmacological (Ablett et al., 1984) manipulations of plasma LNAA levels have been shown to cause the predicted changes in brain tyrosine levels. Probably the most effective way to increase brain tyrosine is to administer the amino acid orally, along with sufficient carbohydrate to elicit insulin secretion and, thereby, to lower plasma levels of the other LNAA (Mauron and Wurtman, 1982).

Recent studies have obtained evidence that a variety of severe stresses [e.g., immobilization (Milakofsky et al., 1985); hemorrhage (Conlay et al., 1985)] can selectively increase the plasma tyrosine ratio. This may reflect a shunting of blood away from the liver, where tyrosine is metabolized, and could serve to increase the amino acid's availability.

Firing Frequency, Tyrosine-Dependence, and Allosteric Changes in Tyrosine Hydroxylase

An additional mechanism by which increased activity can cause catecholaminergic neurons to become tyrosine - sensitive involves kinetic changes in tyrosine hydroxylase that result from its phosphorylation. This process is accelerated when neuronal activity increases. Phosphorylation of tyrosine hydroxylase can be catalyzed by any of several protein kinases, each of which acts selectively on particular amino acids in the enzyme protein (Niggli et al., 1984; Ames et al., 1978).

The enzyme activation occurring when neuronal activity increases (i.e., after <u>in vitro</u> depolarization of rat striatum) is dependent on calcium and calmodulin (El Mestikaway et al., 1983). It increases the enzyme's activity, without changing its affinity for tyrosine or the tetrahydrobiopterin cofactor, nor its susceptibility to end-product inhibition. A different, cAMP-dependent protein kinase can also phosphorylate tyrosine hydroxylase, increasing its affinity for its cofactor (but not tyrosine), and also perhaps decreasing its susceptibility to end-product inhibition (Lovenberg et al., 1975; Harris et al., 1972). Recent evidence suggests that in striatal dopaminergic nerve terminals, the dopamine released following depolarization acts via presynaptic autoreceptors to decrease local cAMP levels; this slows

TABLE 3: Effects of Tyrosine on Catecholamine-Mediated Phenomena

Animal model	Physiological parameter	Tyrosine effect	Reference
Rat	Open field behavior	Reversal of stress-induced inhibition	Lehnert et al., 1984.
SHRs	Blood pressure	Hypotensive	Sved et al., 1979; Yamori et al., 1980; Boss et al., 1983.
Rat (hemorrhaged)	Blood pressure	Hypertensive	Conlay et al., 1981.
Dog	Ventricular arrhythmia	Preventative	Scott et al., 1981.
Rat	Renal hypertension	Hypotensive	Breshnahan et al., 1980.
Aged, anestrous female rats	Estrous cycling	Restored	Linnoila and Cooper, 1976.
Aged mice	Motor activity	Increased	Thurmond and Brown, 1984.
Mice	Swim test immobility	Ameliorated	Gibson et al., 1982.
	Open field behavior	Increased activity	

the phosphorylation of the tyrosine hydroxylase and decreases its activity (El Mestikaway and Hamon, 1985). Hence the physiologic role of the cAMP-dependent protein kinase in striatum may be to suppress tyrosine's hydroxylation in response to prolonged dopamine release. In contrast, the calcium-calmodulin-dependent protein kinase is activated when voltage-gated calcium channels open during membrane depolarization; catecholamine formation thereupon depends on the extent to which the tyrosine hydroxylase happens to be saturated with tyrosine. This, in turn, will depend on the enzyme's Km for tyrosine (which apparently does not change with phosphorylation), and on tyrosine levels within the nerve terminal. The latter have not been measured, but presumably they bear a relationship to whole-brain tyrosine levels (which, in turn, vary with the plasma tyrosine ratio, as discussed above).

Physiological Consequence of Tyrosine Administration

If tyrosine availability does indeed affect brain catecholamine synthesis and release, it should also be expected that it will also influence various behaviors and physiological processes that involve catecholaminergic neurotransmission. Some publications demonstrating such effects are described in Table 3 (Lehnert et al., 1984; Scott et al., 1981; Breshnahan

et al., 1980; Linnoila and Cooper, 1976; Thurmond and Brown, 1984; Gibson et al., 1982). One such catecholamine-dependent process is the control of blood pressure, which is elevated by the release of norepinephrine or epinephrine from sympathoadrenal cells, and either decreased or increased by norepinephrine release within the central nervous system, depending on the locus of this release (Philippu et al., 1980). In SHR's, tyrosine injection causes a marked fall in blood pressure, which is blocked by co-administration of other LNAA's (Sved et al., 1979). Under these conditions, brainstem levels of the major noradrenaline metabolite MHPG-SO4 are elevated. Similar findings are obtained when tyrosine is injected into the lateral ventricles of these animals (Yamori et al., 1980). These observations indicate a central mechanism for tyrosine's antihypertensive effect, [consistent, for example, with enhanced noradrenaline release from locus coeruleus neurons). Tyrosine administration to stressed rats also causes behavioral effects: when given via the diet prior to stress or by injection thereafter, it blocks the stress-induced fall in regional brain NE levels and amplifies the increase in MHPG-SO4; it also blocks such post-stress behavioral changes as diminished locomotor activity and a diminished tendency of the animal to manifest its "curiosity" by standing on its hind legs or poking its nose into a hole (Reinstein et al., 1984; Lehnert et al., 1984). Attempts to determine whether tyrosine may also affect behavior and performance in healthy humans are in their infancy. However, given the extreme non-toxicity of the amino acid, any positive effects that tyrosine is found to exert will almost certainly be useful.

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